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Mazabraud Syndrome in Two Patients: Clinical Overlap With McCune-Albright Syndrome

L. Faivre,[1,2] A. Nivelon-Chevallier,[1] M.L. Kottler,[3] C. Robinet,[1] P. Khau Van Kien,[1] B. Lorcerie,[4] A. Munnich,[2] P. Maroteaux,[2] V. Cormier-Daire,[2] and M. LeMerrer[2]*

[1]*Centre de Génétique, Hôpital d'Enfants, Dijon, France*
[2]*Département de Génétique, Hôpital Necker-Enfants Malades, Paris, France*
[3]*Service de Biochimie Médicale, CHU Pitié-Salpétrière, Paris, France*
[4]*Service de Médecine Interne, Hôpital du Bocage, Dijon, France*

Mazabraud syndrome is a rare sporadic disorder, mainly characterized by bone fibrous dysplasia and intramuscular myxomas. We report here two new cases of Mazabraud syndrome. One of our patients (Patient 1) also had café-au-lait spots and multinodular goiter suggestive of McCune-Albright syndrome. We review the 37 previously reported cases with Mazabraud syndrome and discuss the 6/37 patients with criteria of Mazabraud and McCune-Albright syndromes. Based on the clinical overlap between the two syndromes, we tested the *GNAS1* gene in blood leukocytes and skin fibroblasts of Patient 1, but found no evidence of an activating mutation in the *GNAS1* gene.

KEY WORDS: Mazabraud syndrome; McCune-Albright syndrome; intramuscular myxomas; fibrous dysplasia of bones; *GNAS1* gene

INTRODUCTION

Skeletal fibrous dysplasia and soft tissue myxoma both result from benign proliferation of dysplastic fibrous connective tissue [Reed, 1963] and cells of mesenchymal origin, respectively [Ireland et al., 1973; Heymans et al., 1998]. In 1926, Henschen reported for the first time the association of soft tissue myxomas and fibrous dysplasia [Henschen, 1926], and it was then further delineated by Mazabraud in 1957 [Mazabraud and Girard, 1957]. More than 30 patients have been documented [Cabral et al., 1998]. Among them, patchy cutaneous pigmentation and endocrinopathies have been described. The molecular basis of this condition is unknown, but a hypothesis of postzygotic mutation has been suggested since all cases are sporadic and the distribution of lesions is variable [Aoki et al., 1995].

Similarly, McCune-Albright syndrome (MAS, MIM 174800) is a sporadic condition defined clinically by the combination of three symptoms: fibrous dysplasia of bones, brown pigmented areas of the skin, and various endocrine disorders [Laporte et al., 1961]. The presence of two of three symptoms is sufficient for the diagnosis [Lee et al., 1986]. MAS is caused by mosaicism activating missense mutations of the *GNAS1* gene [Weinstein et al., 1991; Schwindinger et al., 1992; Shenker et al., 1993, 1994; Dötsch et al., 1996] (MIM 139320). Recently, identical mutations have been found in atypical MAS cases [Boston et al., 1994; Malchoff et al., 1994; Tinschert et al., 1999], in bone cells from patients with isolated monostotic fibrous dysplasia [Shenker et al., 1995], as well as in endocrine cells from patients with isolated endocrine tumors [Landis et al., 1989; Suarez et al., 1991; Fragoso et al., 1998].

We report on two new patients with Mazabraud syndrome (MS) and emphasize the overlap with MAS. We tested the *GNAS1* gene in blood lymphocytes and skin fibroblasts of one patient.

CLINICAL REPORTS AND METHODS

Patient 1

A 40-year-old woman was referred for the presence of myxomas and fibrous dysplasia. There was no family history of either of these. Pigmentary changes of the skin were noted at birth. Puberty occurred at a normal age. Her medical history was uneventful until the age of 33, when she presented with a fibrocystic dysplasia of the breast diagnosed by mammography. Two years later she discovered a lump in her left arm. The lump was painful and surgically removed. Pathological studies showed that the tumor was a 3-cm typical intramuscular myxoma. At this time, radiological studies demonstrated a femoral fibrous dysplasia. During the 4 years following arm surgery, three further myxomas, which were causing pain on muscle contraction and growing

*Correspondence to: Dr. M. LeMerrer, Département de Génétique, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France. E-mail: lemerrer@necker.fr

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rapidly, were removed from the left thigh. The largest was 10 cm in diameter. One of them reappeared, necessitating further surgery.

Physical examination showed four masses, located in the left and right thigh muscles, and in the left leg muscle, with a maximum size of 5 cm. They were firm and could not be moved when the muscle was tensed. Joint motion was not painful and a full range of movement was recorded. Posterior bowing of the right femur and leg asymmetry were noted. There was no lymphadenopathy or muscle atrophy, no skin changes or increased warmth over the area of the mass. Skin examination showed multiple, large café-au-lait spots with irregular edges over the back, the right leg (Fig. 1a), and the forehead. Freckles of the lip were noted. There were no facial abnormalities. Endocrine examination revealed a multinodular goiter.

Radiographic examination showed multiple lesions consistent with polyostotic fibrous dysplasia in the left pelvic bones, both femora, and the left tibia and fibula (Fig. 1b,c). An undisplaced fracture of the right femur and a bilateral coxa vara were also noted. Bone density of the skull base and maxilla were increased. Magnetic resonance imaging (MRI) of the leg myxomas revealed that the tumors were homogeneous, hypointense to the muscle on T_1-weighting, and markedly hyperintense on T_2-weighting. Serum calcium and serum phosphate were normal. Hormonal investigations at the time of admission disclosed normal results of thyroid function tests, follicle stimulating hormone (FSH), luteinizing hormone (LH), parathyroid hormone (PTH), growth hormone (GH), and cortisol levels. Ultrasound and ^{99}Tc scan of the thyroid gland were normal.

After 2 years follow-up, the patient complains of an increase in size of the left thigh myxomas, which are painful under pressure.

Patient 2

Patient 2 was first referred at the age of 42 for a worsening fibrous dysplasia and the discovery of masses in the left lower limb. His family history was uneventful and he had two healthy children. At age 18, the diagnosis of diffuse fibrous dysplasia was made after a fracture of the right femur and the left humerus.

At age 47, he presented with a calcaneus fracture. He also had a depression of the cranial vault in the right parieto–occipital region and two large tumors in the posterior right thigh and the left tibia. Skin findings and results of endocrine examinations were normal. Radiographs of the skeleton showed diffuse fibrous dysplasia (Fig. 1e,f), with an increasing number of bone lesions and a right predominance of the lesions. Ultrasound and MRI (Fig. 1d) of the tumors were consistent with myxomas. Endocrine tests were not performed. Tumors were not enlarging and surgery was not deemed necessary.

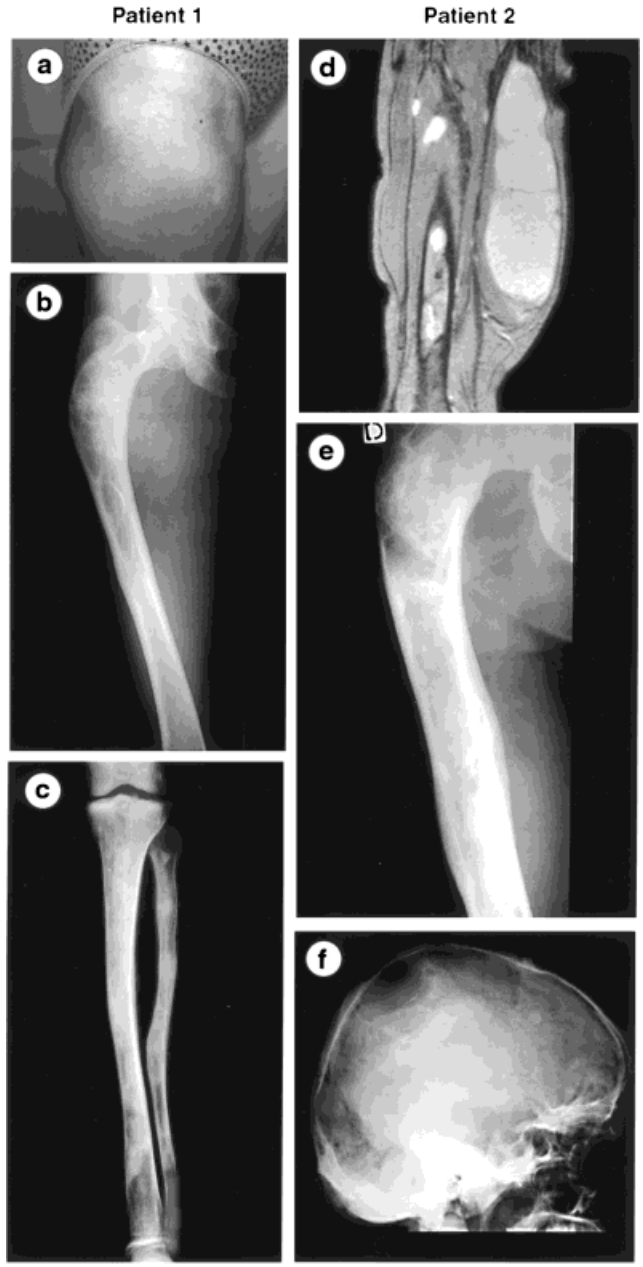

Fig. 1. **a**: Right thigh of Patient 1. Note the large café-au-lait spots with irregular edges. **b,c**: Radiographs of Patient 1. Multiple radiolucent areas throughout the femur and a "ground glass" appearance typical of fibrous dysplasia. The tibia and fibula show bowing throughout the whole length of the diaphysis. **d**: Coronal T_2-weighted MR image of Patient 2, demonstrating a large hyperintense well-defined mass of the right thigh. **e,f**: X-rays of Patient 2. Note the radiolucent areas of the vertex and the parietal bones, the occipital thickening and the irregularity of the skull. The femora is irregular, with areas of osseous remodeling with large cloudy zones of osteolysis and patchy sclerosis. Note the deformity of the upper femur.

Molecular Investigations

DNA was extracted from peripheral leukocytes and from skin biopsies (normal and hyperpigmented areas) by a proteinase K digestion and phenol/chloroform extraction. DNA was amplified using primers (Genset, Paris) synthesized on the basis of the published sequence [Kozasa et al., 1988] and designed to bridge exon 7 to exon 9. F7: 5′-CTGAGCGCTGTGAACACCCC-3′; R9: 5′-GTGAGCAGCGACCCTGATCC-3′. PCR was performed in a total volume of 50 μL containing 150 ng DNA, 250 nM each of primers, 200 μM dNTPs and 1 U

TABLE I. Clinical and Radiological Manifestations of the New Patients With MS and Literature Review

		First symptom		Myxomas	Bone lesions		Skin abnormalities	Endocrine abnormalities	Complications	Comments
	Sex	Type	Age (years)	Number	Characteristics	Uni- or bilateral				
Patient 1	F	My	30	Multiple	Polyostotic	Bilateral	+	Goitery	Pain	Breast dysplasia
Patient 2	M	FD	18	Multiple	Polyostotic	Bilateral	–	–	Fractures	–
Literature (n=37)	15M 22F	FD(23) My(14)	FD(16.7) My(42.3)	Unique (12) Multiple (15)	Polyostotic (32) Monostotic (5)	Bilateral (20) Right (13) Left (4)	13/37	8/37	Fractures (6) Pain (5) Osteosarcoma (3) Recurrence (2)	Breast fibrosarcoma (1) Uterus fibroadenomas (1)

My: Myxerma, FD: Fibrous dysplasia.

Taq Polymerase (Pharmacia Biotech, France). Thirty-five cycles were performed at 95°C, 59°C, and 70°C for 1 min each. PCR products (537 bp) were purified on Microcon-100 columns (AMICON, Beverly, MA, USA). Sequencing was carried out on both strands using the Big Dye Terminator sequencing kit and an ABI PRISM 377 DNA sequencer (Perkin Elmer, Roissy, France) according to the manufacturer's instructions. Sequencing of each fragment identified mutations neither within the PCR products nor at codons 201 (exon 8) and 227 (exon 9).

DISCUSSION

Our two patients present the characteristics of MS, namely skeletal fibrous dysplasia and soft tissue myxomas. MAS is defined by the presence of at least two of the three following symptoms: skeletal fibrous dysplasia, brown pigmented areas of the skin, and endocrine dysfunctions [Lee et al., 1986]. Patient 1 has signs of both syndromes (i.e., café-au-lait spots and multinodular goiter suggestive of MAS).

Among the 37 previously reported patients with MS (Table I) [Henschen, 1926; Mazabraud and Girard, 1957; Heinemann and Woerth, 1958; Mazabraud et al., 1967; Roze et al., 1967; Wirth et al., 1971; Ireland et al., 1973; Logel, 1976; Lever and Pettingale, 1983; Biagini et al., 1987; Prayson and Leeson, 1993; Aoki et al., 1995; Cabral et al., 1998; Szendrói et al., 1998], a skewed sex ratio toward females (59%) was observed. The first presenting symptom was fibrous dysplasia in 62% of cases. The mean age at diagnosis was 24.6 years (range 1–55), but differed considerably depending on the first presenting symptom. Isolated intramuscular myxomas were generally single [Ireland et al., 1973; Heymans et al., 1998], but in MS two or more intramuscular myxomas were found in 68% of cases. Similarly, in contrast with classical fibrous dysplasia [Reed, 1963], bone lesions were more often polyostotic (86%) and bilateral (54%). The long bones were most frequently involved. Complications of the disease included fractures (16%), pain (14%), osteosarcoma (8%), and recurrence of myxomas after surgery (5%). Three cases of gynecological tumors have been reported, but it is difficult to know whether or not these tumors are a part of the disease. Area of hyperpigmentation of the skin and endocrine abnormalities, including precocious puberty (four cases), goiter (four cases), hyperthyroidism (two cases) or hypothyroidism (one case), and diabetes mellitus (one case), were noted, respectively,

TABLE II. Findings in Patients With Criteria of Both MAS and MS

References	Sex	First symptom	Age at first symptom	Myxoma	Fibrous dysplasia	Skin abnormalities	Endocrine abnormalities
Heinemann et al., 1958	F	FD	18	Multiple	Polyostotic	+	Goiter
Laporte et al., 1961	F	FD	12	Unique	Polyostotic	+	Precocious puberty Hyperthyroidism
Mazabraud et al., 1967	M	FD	Infancy	Multiple	Polyostotic	+	Precocious puberty
Roze et al., 1967	F	FD	20	Multiple	Polyostotic	+	Precocious puberty
Logel, 1976	F	FD	Childhood	Multiple	Polyostotic	+	Diabetes mellitus Hyperthyroidism with goiter
Lever et al., 1983	F	FD	1	Unique	Polyostotic	+	Precocious puberty

in 35% and 21% of cases. Both skin changes and endocrine abnormalities were noted in 16% of patients with MS [Heinemann and Woerth, 1958; Laporte et al., 1961; Mazabraud et al., 1967; Roze et al., 1967; Logel, 1976; Lever and Pettingale, 1983], illustrating the overlap with MAS. It is worth noting that two patients [Logel, 1976; Lever and Pettingale, 1983] were not reported as MS, but as MAS with myxomas. The six cases with full criteria of both MS and MAS are summarized in Table II.

The hypothesis that MAS and MS could be a different expression of the same disease has been postulated [Roze et al., 1967; Logel, 1976]. MAS is caused by activating missense mutations at codon 201 of the *GNAS1* gene [Weinstein et al., 1991; Schwindinger et al., 1992; Shenker et al., 1993, 1994; Dötsch et al., 1996]. The same mutations have also been found in atypical cases of MAS [Boston et al., 1994; Malchoff et al., 1994; Tinschert et al., 1999], isolated monostotic or polyostotic fibrous dysplasia [Shenker et al., 1995], and even in sporadic endocrine tumors, such as thyroid [Suarez et al., 1991], pituitary [Landis et al., 1989], ovarian, and testicular Leydig cell tumors [Fragoso et al., 1998]. Similarly, an activating missense mutation at codon 227 of the *GNAS1* gene has been reported in pituitary tumors [Clementi et al., 1990; Fragoso et al., 1998]. These mutations lead to a constitutive activation of adenylate cyclase resulting in increased signaling through the cyclic AMP (cAMP) pathway. Molecular biology studies on blood leukocytes in Patient 1 found no evidence of an activating mutation in the *GNAS1* gene at codons 201 and 227. However, the tested tissues in our patient were blood and fibroblasts, and a mosaicism was not ruled out by these studies. A *GNAS1* mutation was always found in patients with MAS when pathogenic tissues were tested, but not identified in 6/12 blood leukocytes and in 3/4 skin fibroblasts tested (normal and hyperpigmented area) [Weinstein et al., 1991; Schwindinger et al., 1992; Shenker et al., 1993, 1994; Boston et al., 1994; Malchoff et al., 1994; Dötsch et al., 1996; Tinschert et al., 1999]. Similarly, in isolated fibrous dysplasia, *GNAS1* mutations were only identified in bone, but not in blood samples [Shenker et al., 1995].

Only the analysis of myxomas or bone cells in MS patients or sequencing of the entire *GNAS1* gene will permit conclusions on whether or not the *GNAS1* gene is the Mazabraud-causing gene.

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